Aziridination of Alkenes using 3-Acetoxyaminoquinazolin-4(3*H*)ones: Nucleophilic Attack by the Acetoxyamino Group on Ester-substituted Allylic Alcohols

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Allylic alcohols **5** and **7** and their acetates **6** and **8** are aziridinated using 3-acetoxyaminoquinazolinone **1**; the preferred sense of diastereoselection in aziridination of **5** is inverted in aziridination of its acetate **6** whereas the preferred sense of diastereoselection from **7** is retained in aziridination of its acetate **8**; this is interpreted as evidence for nucleophilic attack by the acetoxyamino nitrogen of **1** on the alkene with hydrogen bonding between the hydroxyl and *N*-acetoxy group present in aziridination of **5** but absent in the case of **7**.

3-Acetoxyaminoquinazolinones *e.g.* **1** (QHNOAc) are nitrogen analogues of peroxyacetic acid (HOOAc); in their reactions with alkenes these reagents bring about aziridination and epoxidation respectively by what appear to be similar mechanisms.[1] The reaction of cyclohexenol with 3-acetoxyamino-2-ethylquinazolinone **1**, like the reaction of this allylic alcohol with peroxybenzoic acid, gives the *cis*-diastereoisomer selectively [Scheme 1(*a*)]. However, whereas using **1**, aziridination of cyclohexenyl acetate is highly *anti*-diastereoselective (albeit low-yielding), epoxidation using peroxybenzoic acid is not[2] [Scheme 1(*b*)].

A further major difference between aziridination using **1** and epoxidation using peroxyacids is that whereas the aziridination of certain α,β-unsaturated esters and ketones is high-yielding, epoxidation, in general, is not.

We have prepared a number of ester-bearing allylic alcohols **2** and **3** and their acetates and have examined the diastereoselectivity of their aziridinations using 3-acetoxyaminoquinazolinone **1**.

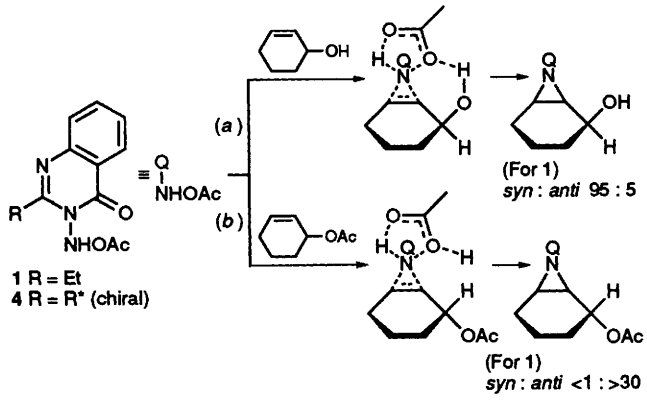
Our aim in this study was to obtain a description for the preferred transition state geometry (TSG) for these substrate-controlled aziridinations: it was anticipated that this TSG could then be applied to the rational design of the chiral 2-substituent in 3-acetoxyaminoquinazolinones **4** for reagent-controlled diastereoselective aziridinations of achiral substrates.

The diastereoselectivities obtained in aziridinations of **5–8** are shown in Scheme 2.† These aziridinations were carried out under standard conditions by using a solution of **1** prepared at −20 °C in dichloromethane, adding the allylic alcohol or allylic acetate (1.4 mol equiv.) and allowing the solution to warm to room temp. Aziridine product ratios were measured from NMR spectroscopy (300 MHz) of the crude reaction mixtures and assignments of signals confirmed by isolation of pure diastereoisomers by chromatography.

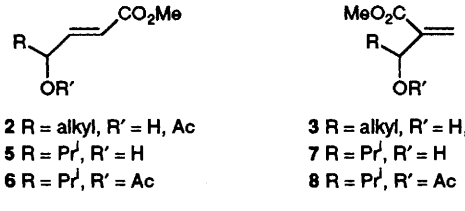
Comparison of the ratio of diastereoisomeric aziridines in Scheme 2 produced from **5** and **6** (2.5 : 1 versus 1 : 3) reveals that the major diastereoisomer **9** from **5** has the same relative configuration as the minor diastereoisomer **11** from **6**, *i.e.* the sense of diastereoselection is *inverted* in aziridination of the allylic acetate **6** by comparison with the allylic alcohol **5**. The relative configuration of the major aziridine alcohol diastereoisomer **9** was proved by X-ray crystallography [(Fig. 1(*a*)].‡§ Correlation between the aziridines obtained from **5** and **6** was established by acetylation of alcohols **9** and **10** which gave **11** and **12** respectively. The diastereoisomeric relationship between **9** and **10** was confirmed by oxidation of **9** to the corresponding ketone which gave **9** and **10** in a ratio of 2.5 : 1 on reduction with sodium borohydride.

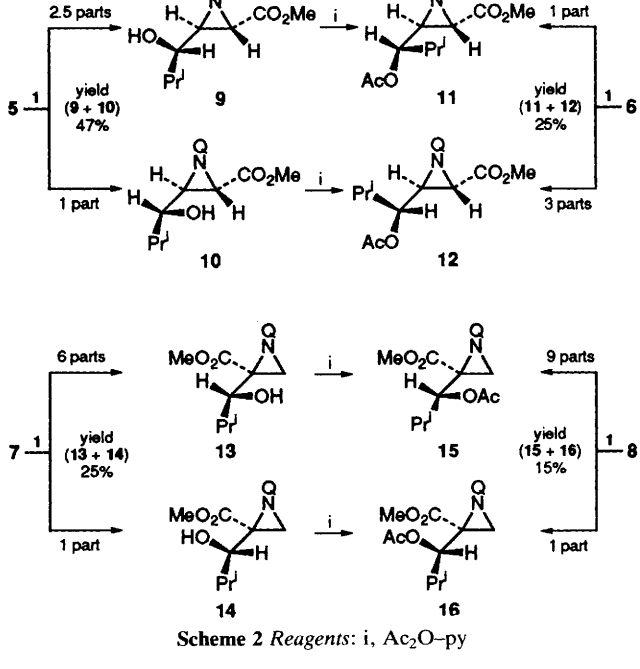
Inversion of the sense of diastereoselection in aziridination of allylic alcohol **5** by comparison with that of its acetate **6** is analogous to that previously described in Scheme 1(*a*) using cyclohexenol and its acetate [Scheme 1(*b*)]. We assume that hydrogen bonding is present in a transition state for formation of the major diastereoisomer **9** from **5** which resembles that in Fig. 2(*a*).

The important features of this transition state are (*a*) the alkene and quinazolinone ring are contained in parallel planes (*b*) the (*S-cis*-configured) ester carbonyl oxygen lies under, and interacts favourably with, the quinazolinone carbonyl carbon (C-4)[3] (*c*) the acetoxyamino nitrogen is functioning as a nucleophile [N–(C-3) bond formation is running ahead of (C-2)–N bond formation] (*d*) S_N2-like attack on the acetoxyamino nitrogen occurs with assistance by hydrogen bonding



Scheme 1





Scheme 2 *Reagents*: i, Ac_2O–py

to the departing acetoxy group (*e*) the isopropyl group occupies the somewhat less hindered 'outside' position.

For aziridination of allylic acetate **6**, in which hydrogen bonding is absent, a transition state resembling that in Fig. 2(*b*) would be similar to that in Fig. 2(*a*) but the existing chiral centre would be of inverted configuration (the allylic alcohol **5** and acetate **6** are racemic); orientation of the allylic acetoxy group as shown would maximise electron-withdrawal by σ*–π* overlap and facilitate nucleophilic attack at C-3.

The major diastereoisomer obtained from aziridination of the isomeric allylic alcohol **7** (Scheme 2) was identified as **13** from X-ray crystallography [Fig. 1(*b*)].§ As above, the diastereoisomeric relationship between alcohols **13** and **14** was confirmed by reduction of the corresponding ketone, prepared by oxidation of **13** and the relative configuration of the acetates **15** and **16** (Scheme 2) from aziridination of the allylic acetate **8** was established by acetylations of the corresponding alcohols.

From the aziridine diastereoisomer ratios shown in Scheme 2 for **13** : **14** and for **15** : **16** (6 : 1 *vs.* 9 : 1) it is clear that the sense of diastereoselection is *retained* in aziridinations of allylic alcohol **7** and its acetate **8**. This contrasts with the results described above for aziridination of **5** and its acetate **6** (Scheme 2) and of cyclohexenol and cyclohexenyl acetate (Scheme 1).¶

The conclusion we draw from this difference is that hydrogen bonding is absent in the transition state for formation of the preferred diastereoisomer **13**. If the essential features of the TSG in Fig. 2 are applied to the formation of **13** (Fig. 3), it is clear that the requirement for S_N2 displacement on nitrogen precludes the possibility of hydrogen bonding. In Fig. 3 the isopropyl group is in the sterically least-hindered position and assists in nucleophilic displacement of the *N*-acetoxy group (σ–π overlap) and the hydroxyl group occupies an 'inside' position to avoid electrostatic interaction with ester oxygen.

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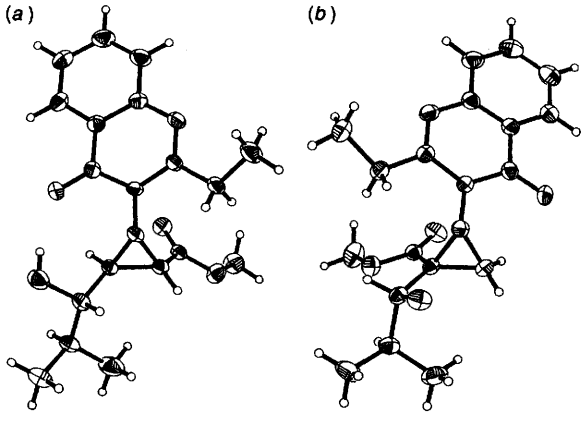

Fig. 1 X-Ray Crystal Structures of **9** (*a*) and **13** (*b*)

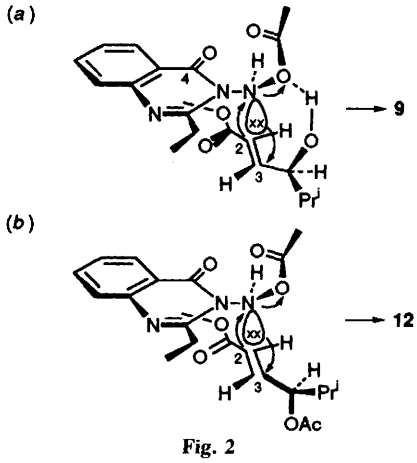

Fig. 2

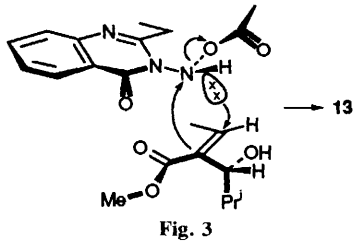

Fig. 3

Footnotes

† All new compounds reported have been fully characterised.

‡ Assignments of relative configuration to all the alcohols and their acetates in this paper are supported by correlation of the relative chemical shift of the Pr^{i}C*H*O– protons in each pair of diastereoisomers.

§ *Crystal data*: Data for **9** and **13** were measured on a Siemens P4 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å) at 293 K with an ω-scan technique. The data were corrected for Lorentz and polarisation effects. The structures were solved by direct methods and refined by full-matrix least squares using the SHELXTL-PC program package. (G. M. Sheldrick, SHELXTL-PC Release 4.2 Siemens Analytical X-ray Instruments Inc., Madison, WI, 1991). For **9**: $C_{18}H_{23}N_3O_4$, M = 345.4, triclinic, space group $P\bar{1}$, a = 9.379 (2), b = 9.760 (1), c = 10.994 (2) Å, α = 85.61 (1), β = 69.42 (1), γ = 75.38 (1)°, V = 911.6 (3) Å^3, Z = 2, D_c = 1.258 Mg m^{-3}, F(000) = 368, μ = 0.09 mm^{-1}, crystal dimensions 0.32 × 0.24 × 0.09 mm. 3501 unique data were measured with 1867 having $F > 4\sigma(F)$ regarded as observed. All non-hydrogen atoms were refined as anisotropic. The hydroxyl hydrogen atom bonded to C(2) was located from a difference Fourier map, all other hydrogen atoms were included in calculated positions (C–H = 0.96 Å). Final R = 0.061 and R_w = 0.063 for 227 variables, $(\Delta/\sigma)_{max}$ = 0.006. For **13**: $C_{18}H_{23}N_3O_4$, M = 345.4, orthorhombic, space group *Iba*2, a = 8.244 (4) b = 41.587 (13), c = 10.607 (9) Å, V = 3637 (4), Z = 8, D_c = 1.262 Mg m^{-3}, F(000) = 1472, μ = 0.09 mm^{-1} crystal dimensions 0.68 × 0.34 × 0.28 mm. 2762 Unique data were measured with 2407 having $F > 4\sigma(F)$ regarded as observed. All non-hydrogen atoms were refined as anisotropic. The hydroxyl hydrogen was not located or include in the refinement, all other hydrogen atoms were included in calculated positions (C–H = 0.96 Å). Final R = 0.052 and R_w = 0.069 for 235 variables, $(\Delta/\sigma)_{max}$ = 0.036. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue no. 1.

¶ We have also carried out aziridinations on analogous compounds **2** (R = Et, R′ = H), **2** (R = Et, R′ = Ac), **3** (R = CH_2Pr^i, R′ = H), **3** (R = CH_2Pr^i, R′ = Ac) and **3** (R = Pr, R′ = H). Although the diastereoisomer ratios are slightly less disparate, the changes in the sense of diastereoselection are the same as those reported for **5**–**8**.

References

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2 R. S. Atkinson and B. J. Kelly, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1515.

3 R. S. Atkinson and J. R. Malpass, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2242.